## REMARKS

### I. Status of claims

Claims 1, 2, and 6 are amended.
Claims 36 and 37 are new.
Claims 3-5, and 7-35 were previously withdrawn.
Claims 1, 2, 6, and 36-37 are pending.

Claims 36 and 37 have support throughout the specification and in the originally filed claims 34-35.

### II. New Species Election

Applicants affirm election of "Gadd45 protein" as a species. In addition, in response to the examiner's additional request on page 2 of the Action, applicants further elect JNKK2 as a species for prosecution on the merits with respect to a target within the JNK pathway.

### III. Sequence identifiers

A preliminary amendment accompanying the sequence listing was filed on February 17, 2004. The examiner requested sequence identifiers for "Peptide 1 and Peptide 7" mentioned in the specification. Peptides 1 and 7, as mentioned in the specification do not have accompanying sequence descriptions and therefore do not require SEQ ID NOS. The boundaries 132-156 and 220-234 of MKK7/JNKK2 and their accompanying sequences are within the molecule with a sequence identification number i.e., SEQ ID NO: 50 (full length JNKK2).

### IV. Pending claims satisfy § 112 second paragraph requirements.

On page 4 of the Action, the examiner objected to the phrase "within the JNK pathway". Claim 1 has been amended to replace "target within the JNK pathway" with "an agent that interacts with Gadd45β". Claim 2 is further amended. Therefore, claim 1 and its dependent claims particularly point out and distinctly claim the subject matter under §112 second paragraph. Applicants request allowance of the pending claims.

**V. Pending claims satisfy § 112 first paragraph enablement requirements.**

On pages 5-9 of the Action, the examiner rejected claims 1, 2, and 6 under §112 first paragraph enablement requirements. Claims 1, 2, and 6 have been amended.

The examiner admits that the specification is:

> enabling for an *in vitro* method of modulating JNK pathway leading to program cell death.

Office Action, page 5.

but doubts enablement of *in vivo* methods regarding JNK activation by Gadd45β.

The examiner acknowledges that:

> the specification further teaches that Gadd45β binds to and inhibits JNKK2, thereby down regulating the JNK pathway in vitro (para 00072).

Office Action, page 5

The examiner acknowledges the role of JNK in apoptosis, and the role of apoptosis in oncogenesis. The present invention relates that inhibition of Gadd45β by an agent, increases JNK activity, thereby leading to increased apoptosis. The same mechanism has been confirmed *in vivo* in a mouse model (Exhibit A). It is a "physiologic activity (par. 0018)" as requested in the Office Action, page 6.

In addition, in the specification, FIGS. 19-20 show physical interaction between Gadd45β and kinases in the JNK pathway in 293 cells. FIG. 21 shows Gadd45β inhibits JNKK2 activity *in vitro*. FIG. 22A-B shows Gadd45β inhibits JNKK2 activity in 3DO cells. FIGS. 23-27 show that distinct polypeptide regions in JNKK2 and Gadd45β interact. These figures and accompanying description in the specification demonstrate that Gadd45β interacts with JNKK2 and further regulates JNKK2 activity. These data illustrate that Gadd45β modulates JNK pathway by regulating JNKK2 activity.

Furthermore, a 37 C.F.R §1.132 Declaration from Dr. Guido Franzoso (Exhibit A), a co-inventor of the present application, clearly demonstrates that Gadd45β modulation of the JNK pathway extends to *in vivo* models. Specifically, Exhibit A demonstrates that Gadd45β modulates JNKK2 activity *in vivo*, in a mouse model. Experiments involving Gadd45β knock-out mice are shown in accompanying Exhibit A. Gadd45β knock-out mice do not have functional Gadd45β and therefore cannot modulate JNK activity. JNK activation leads to cell death in mice following hepatectomy.

The data from Gadd45β knock-out mice model and JNK2 knock-out mice model as described in the 1.132 declaration and Exhibit A provide substantial evidence that Gadd45β is a modulator of JNK pathway in regulating cell death *in vivo*. The mouse model further supports the results obtained earlier from cell culture and *in vitro* studies in the specification that demonstrated direct Gadd45β-JNKK2 interaction and modulation of JNK pathway. This experimental proof confirms the "nexus" or reasonable correlation to *in vivo* efficacy established by the *in vitro* results.

The specification also discloses that an agent, e.g., a cell permeable peptide that includes a Gadd45β binding region on JNKK2 activates cell death and thereby modulates JNK activity. Therefore, the pending claims are enabled.

The examiner presents a lengthy discussion of the unpredictability of cancer therapies. (Office Action, pages 8-10). There are no claims pending to cancer treatment, so this discussion is not on point. Also, it is not necessary to show that a cancer treatment works, even were it claimed. As the courts have reminded us, the PTO is not the FDA. It is the FDA's role to decide if cancer therapies are effective.

**VI. Pending claims satisfy § 112 first paragraph written description requirements.**

On pages 10-13 of the Action, the examiner rejected claims 1, 2, and 6 under §112 first paragraph written description requirements. There is a lengthy discussion of what is needed to claim a molecule. However, pending claims are to a method, not to a molecule. Also, claims 1, 2, and 6 have been amended. The specification as filed disclosed a working example that a peptide can modulate the JNK pathway and regulate cell death. A cell permeable peptide is an

agent that modulates the JNK pathway by suppressing Gadd45β-inactivation of JNK signalling. Amended claims 1, 2, and 6 reflect that finding. The specification also describes other agents such as anti-sense, ribozymes, and mimetics that are capable of modulating JNK pathway by interfering with the Gadd45β-JNK interaction. Therefore, pending claims and the specification as filed satisfy the written description requirements.

**VII. Reinhard et al. does not anticipate claim 1.**

On pages 13-14 of the Action, the examiner rejected claim 1 under §102 (b) as being anticipated by Reinhard et al. (US 6,492,112).

It is well known that to anticipate, publications must teach each claimed element. Reinhard teaches the MKK7 (JNKK2) protein. Reinhard does not teach or suggest Gadd45β's effect on JNK signalling. Reinhard does not teach selecting a target within a JNK pathway that interacts with or is modulated by Gadd45β. Prior to the priority date of the provisional application, it was not known that Gadd45β interferes with the JNK pathway. Reinhard does not disclose this nexus between Gadd45β and JNK signaling. Also, the binding regions of Gadd45β on JNKK2 were not known and are disclosed in the present application.

To anticipate, a single reference must teach all the elements of the claims. *RCA Corp v. Applied Digital Data Sys., Inc.*, 221 USPQ 385, 388 (Fed. Cir. 1984). A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Reinhard does not teach all the elements of claim 1 and therefore is not an anticipatory reference. Applicants request allowance of pending claims.

**VIII. Double patenting**

If any of the pending claims were found to be allowable, applicants will timely file terminal disclaimers to overcome the provisional double patenting rejection in view of U.S. Ser. No. 10/263,330.

No other fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (21416-94575).

Respectfully submitted,

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